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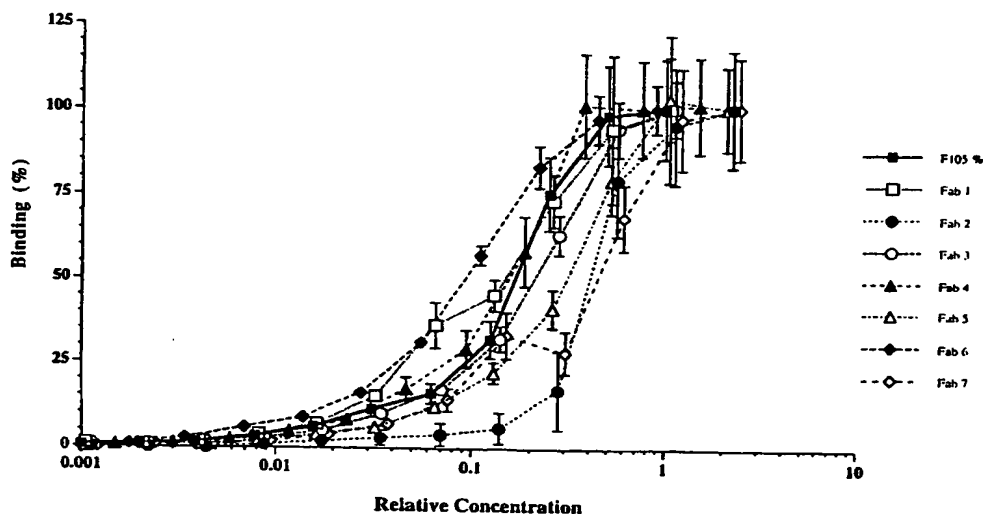
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(54) Title: HUMAN MONOCLONAL ANTIBODIES TO HIV-1 ENVELOPE GLYCOPROTEIN GP120



(57) Abstract: This invention relates to 21 monoclonal antibodies to HIV-1 gp120 which were isolated from three Fab libraries prepared from RNA isolated from the lymph node of a type 1 human immunodeficiency virus (HIV-1) seropositive individual. Of the 21 antibodies, seven recognize the CD4 binding site of gp120, eight recognize the V3 loop and six recognize an as yet unidentified epitope of gp120. This invention further relates to diagnostic methods which utilize the antibodies and to pharmaceutical compositions which employ these antibodies therapeutically and prophylactically.

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TITLE OF THE INVENTION

HUMAN MONOCLONAL ANTIBODIES
TO HIV-1 ENVELOPE GLYCOPROTEIN GP120

FIELD OF THE INVENTION

The present invention relates to human monoclonal antibodies to type 1 human immunodeficiency virus (HIV-1) envelope glycoprotein gp120. The present invention also relates to the phage display libraries from which the antibodies were isolated. This invention further relates to diagnostic methods and to pharmaceutical compositions which employ these antibodies therapeutically and prophylactically.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV), a member of the lentivirus family of animal retroviruses, is the causative agent of Acquired Immune Deficiency Syndrome (AIDS). To date, two closely related types of HIV, type 1 (HIV-1) and type 2 (HIV-2), have been identified and characterized on the molecular level. In addition to the typical retrovirus genes such as *gag*, *env* and *pol*, the HIV genome also includes *vpr*, *vif*, *tat*, *rev*, *nef* and *vpu* genes which regulate viral production in various ways.

Many antibodies immunoreactive with various proteins encoded by HIV have been isolated and these antibodies provide a useful tool for the diagnosis of HIV. However, given the strain heterogeneity of the HIV viruses, there continues to be a need to identify large numbers of additional human antibodies to HIV. In addition, the study of large numbers of human antibodies to HIV would accelerate the development of vaccines against HIV.

Recent advances in recombinant antibody technology have greatly increased the ease with which antibodies can be modified to manipulate their specificity and binding characteristics. The most promising of these advances has been the construction of antibody phage display libraries from variable heavy and light chain antibody genes using a phage display vector specifically designed for the expression of antibody fragments to an antigen (2, 16). From such libraries, large

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- numbers of human monoclonal antibodies to an antigen of choice including HIV-1, can be cloned and isolated.

The HIV *env* gene encodes two envelope glycoproteins, gp120 and gp41, and the binding of gp120 to the CD4 molecule on the surface of a primate T cell or mononuclear phagocyte is the first step during an HIV infection.

Comparison of different HIV-1 isolates have revealed that the structure of gp120 can be divided into five conservative domains (C1 through C5) and five variable domains (V1 through V5) (17). The third variable domain (V3 loop) and the CD4 binding site on the gp120 protein have been identified as the principle neutralizing determinants of HIV-1.

In the present invention, a phage display vector for the expression of human Fabs (20, 21) was used to construct a series of Fab libraries from RNA isolated from the lymph node of a type 1 human immunodeficiency virus (HIV-1) seropositive individual undergoing surgery for lymph-adenopathy and twenty-one human monoclonal antibodies to the HIV-1 gp120 protein were selected from these libraries.

SUMMARY OF THE INVENTION

The present invention relates to human monoclonal antibodies to the HIV-1 envelope glycoprotein gp120 or peptide fragments thereof. In particular, the present invention relates to the isolation and characterization of 21 monoclonal antibodies, seven of which recognize the CD4 binding site of gp120, eight of which recognize the V3 loop and six of which recognize an as yet unidentified epitope of gp120.

The invention also relates to nucleic acid molecules encoding the heavy and light chain immunoglobulin variable region amino acid sequences of the 21 antibodies to the HIV gp120 protein.

The invention further relates to diagnostic methods which utilize these human monoclonal antibodies to screen for the presence of HIV in biological samples.

The invention also relates to the use of these human monoclonal antibodies as diagnostic and therapeutic reagents, and to pharmaceutical compositions which comprise these human monoclonal antibodies.

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As these antibodies were isolated from three Fab phage display libraries prepared from lymph node RNA isolated from an HIV-1-seropositive patient, the invention also relates to the three Fab phage display libraries. These libraries provide a tool for identifying additional human antibodies to HIV-1 or to other pathogens that the individual from whose RNA the libraries were prepared may have been exposed to.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows deduced heavy chain variable region amino acid sequences for Fabs 1-7.

Figure 2 shows deduced light chain variable region amino acid sequences for Fabs 1-7.

Figure 3 shows alignment of VH DNA sequences for Fabs 1-7 with the nearest described germline sequences.

Figure 4 shows alignment of Vk DNA sequences for Fabs 1-7 with the nearest described germline sequences.

Figure 5 shows the relative binding of biotinylated Fab fragments to gp120 as measured by ELISA in a 2-fold dilution series. Data points represent the mean of 4 determinations and error bars are the standard error of the mean.

Figure 6 shows competition of the binding of biotinylated Fab fragments to recombinant gp120 in ELISA by recombinant F105 Fab. Data points represent the mean of 4 determinations and error bars are the standard error of the mean.

Figure 7 shows competition of the binding of biotinylated Fab fragments to recombinant gp120 in ELISA by recombinant CD4. Data points represent the mean of 4 determinations and error bars are the standard error of the mean.

Figure 8 shows competition of binding of biotinylated Fabs 1-7 to recombinant gp120 in ELISA by each of the other unbiotinylated Fab fragments. Data points represent the mean of 4 determinations and error bars are the standard error of the mean.

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Figure 9 shows binding of biotinylated Fabs 1-7 to HIV-1 lysates of different strains of HIV-1 as measured by ELISA. Data points represent the mean of 4 determinations and error bars are the standard error of the mean.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to human monoclonal antibodies to HIV-1 gp120, where the antibodies are isolated as Fab fragments from three Fab phage display libraries prepared from lymph node RNA isolated from an HIV-1-seropositive patient. The phrase "antibody" as used throughout the specification and claims includes immunoglobulin molecules (i.e. two Fab fragments and one Fc fragment) and antigen binding fragments of intact immunoglobulin molecules such as Fab fragments. Methods for producing an intact immunoglobulin from isolated Fab fragments by combining Fab fragments with an Fc domain are known to those of skilled in the art.

In particular, the present invention relates to twenty-one human monoclonal antibodies having specified heavy (H) and light (L) chain immunoglobulin variable region amino acid sequences in pairs (H:L) which confer the ability to bind to specific epitopes on the gp120 of HIV-1.

The present invention therefore relates to the heavy chain immunoglobulin variable region amino acid sequences shown in the sequence listing as SEQ ID NO: 43 through SEQ ID NO: 49, SEQ ID NO: 5-7 through SEQ ID NO: 64, and SEQ ID NO: 73 through SEQ ID NO: 78, and the light chain immunoglobulin variable region amino acid sequences shown in the sequence listing as SEQ ID NO: 50 through SEQ ID NO: 56, SEQ ID NO: 65 through SEQ ID NO: 72, and SEQ ID NO: 79 through SEQ ID NO: 84.

In one embodiment, the human monoclonal antibody of this invention immunoreacts with the CD4 binding site of gp120 protein of HIV-1, and has a heavy chain amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 43 through SEQ ID NO: 49, and a light chain immunoglobulin variable region amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 50 through SEQ ID NO: 56.

In another embodiment, the human monoclonal antibody of this invention immunoreacts with the V3 loop of gp120 protein of HIV-1, and has a heavy

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- chain amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 57 through SEQ ID NO: 64, and a light chain immunoglobulin variable region amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 65 through SEQ ID NO: 72.

5 The present invention also relates to nucleic acid molecules encoding the heavy and light chain immunoglobulin variable region amino acid sequences of this invention where these sequences are shown in the sequence listing as SEQ ID NO: 1 through SEQ ID NO: 42 (SEQ ID NO: 1 encodes SEQ ID NO:43; SEQ ID NO: 2 encodes SEQ ID NO. 44, etc.).

10 Of course, due to the degeneracy of the genetic code, variations are contemplated in the sequences shown in SEQ ID NO: 1 through SEQ ID NO: 42 which will result in nucleic acid sequences that are capable of directing production of antibodies that are identical to the antibodies encoded by the sequences shown in SEQ
15 ID NO: 1 through SEQ ID NO: 42. It should be noted that the DNA sequences set forth above represent a preferred embodiment of the present invention.

20 The present invention also relates to human antibodies comprising an Fab fragment derived from a human monoclonal antibody of this invention and the human Fc domain derived from an IgG subtype. The intact immunoglobulin IgG molecules are preferable to immunoglobulin molecules containing Fab fragments alone.

25 The present invention also relates to the three Fab phage display libraries from which the human monoclonal antibodies of this invention were isolated. These phage display libraries have been deposited with the American Type Culture Collection (ATCC). The ATCC accession numbers for the phage display libraries L938, L939 and L944 are PTA-193, PTA-194 and PTA-195, respectively.

30 The invention further relates to methods of making human monoclonal antibodies from the phage display libraries L938, L939 and L944.

35 In a preferred embodiment, the method for isolating a human monoclonal antibody from these phage display libraries involves (1) using immunoaffinity techniques such as panning to select phage particles that immunoreact with a preselected antigen; (2) transforming bacteria with the selected phage particles; (3) preparing and analyzing the phagemid DNA from the colonies recovered; and (4)

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- expressing and purifying soluble Fab fragments from clones of interest for further analysis.

By using the method disclosed above, additional human monoclonal antibodies to HIV-1 or to any other pathogens that may exist in the individual from whose RNA the libraries were prepared can be isolated from the phage display libraries of this invention.

The invention also relates to the use of these human monoclonal antibodies as diagnostic agents.

The antibodies can be used as an in vitro diagnostic agent to test for the presence of HIV-1 in biological samples. In one embodiment, a sample such as biological fluid or tissue obtained from an individual is contacted with a diagnostically effective amount of one or more of the human monoclonal antibodies of this invention under conditions which will allow the formation of an immunological complex between the antibody and the HIV-1 antigen that may be present in the sample. The formation of an immunological complex which indicates the presence of HIV-1 in the sample, is then detected by immunoassays. Such assays include, but are not limited to, radioimmunoassays, Western blot assay, immunofluorescent assay, enzyme immunoassay, chemiluminescent assay, immunohistochemical assay and the like.

In a preferred embodiment, a human monoclonal antibody which is cross-reactive with multiple HIV strains is used for diagnosing HIV-1. Of the 21 antibodies disclosed in this invention, preferred antibodies are Fabs 1, 2 and 4 which are immunoreactive with all three isolates of HIV-1 tested (IIIb, Ba-L and MN), and Fabs 5, 6, and 7 which are immunoreactive with two of the three isolates of HIV-1 tested.

As the human monoclonal antibodies of this invention may possess the ability to neutralize HIV-1 isolates, the invention also relates to the use of the antibodies of the invention in passive immunotherapy of HIV infection.

To determine whether the twenty-one antibodies described in the Examples or any other antibodies isolated from the phage display libraries L938, L939 and L944 neutralize bound HIV-1 viruses, different neutralization assays may be employed. In a preferred method, neutralization is measured as the ability of the antibody to inhibit HIV-1 infection. In this method, target cells are incubated with

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- o HIV-1 in the presence of the antibody to be tested, and the degree of infection is assessed after at least about 5 days in culture by immunofluorescence staining for HIV-1 to assess percent of HIV-1 positive cells. Target cells can be any HIV-1 susceptible cells, although H9 cells are preferred. Well-characterized HIV-1 neutralizing antibodies are run in parallel as controls. Neutralizing antibody titer are defined as the reciprocal of the monoclonal antibody concentration at which infectivity levels are 60% of control following normalization of the data to control values.

When used in passive immunotherapy, the patient is administered a therapeutically effective amount of one or more neutralizing human monoclonal antibodies. The passive immunotherapy of this invention may be practiced on individuals exhibiting AIDS or related conditions caused by HIV infection, or individuals at risk of HIV infection.

A therapeutically effective amount of a human monoclonal antibody for individual patients may be determined by titrating the amount of antibody given to the individual to arrive at the therapeutic or prophylactic effect while minimizing side effects. The effective amount can be measured by serological decreases in the amount of HIV-1 antigens in the individual. The plasma concentration for individuals receiving the treatment is typically between 0.1 ug/ml to 100 ug/ml.

The human monoclonal antibodies of this invention may be administered via one of several routes including, but not limited to intravenous, intraperitoneal, intramuscular, subcutaneous, transdermal and the like.

The present invention therefore relates to pharmaceutical compositions comprising at least one antibody of the invention and a pharmaceutically acceptable carrier where such carriers may include physiologically acceptable buffers, for example, saline or phosphate buffered saline.

The present invention further relates to anti-idiotypic antibodies to the monoclonal antibodies of this invention. In one embodiment, an anti-idiotypic antibody can be prepared by immunizing a host animal with a monoclonal antibody of this invention by methods known to those of skill in the art. To eliminate an immunogenic response to the Fc region, antibodies produced by the same species as the host animal can be used or the Fc region of the administered antibodies can be removed. The anti-idiotypic antibodies produced can be used to prepare

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- pharmaceutical compositions rather than using the monoclonal antibodies of this invention.

The present invention will now be described by way of examples, which are meant to illustrate, but not limit, the scope of the invention.

5

EXAMPLE

Isolation and Characterization of Human Monoclonal Antibodies to the CD-4 binding Site of HIV-1

Materials and Methods

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Construction of Fab phage display vector pL537

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Vector pL537 was constructed from previously described vector pCOMB3 (1, 2) but differs from pCOMB3 in several aspects. More specifically, the cloning of heavy chains has been simplified by the addition of the human IgG1 hinge region, two restriction sites present in human immunoglobulin genes have been removed, and some sequences have included to enhance the expression and ease of Fab purification.

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The Sac-I restriction site, used in vector pCOMB3 for the cloning of light chains, was replaced with a Bgl-II restriction site by using mutagenic PCR primers (SEQ ID NO: 85: CCGCTTA ACTCTAGAACTGACGAGATCTGCATG and SEQ ID NO:86: GTGAAACTGCTCGAGGTCGAC) to amplify and then replace part of vector pCOMB3 from Xho-I and Xba-I. Sac-I sites occur in the human Ck gene, and in all human VH_{IV} family genes. The cloning of Fd fragments was changed by including part of the human IgG1 hinge region, and using Sfi-I in place of Spe-I to clone these genes. This was done because of previous observation that Spe-I sites occur with a frequency of approximately 25% in human V_H genes, though they are rarely found in germline genes (13).

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The heavy chain leader sequence was changed by inserting a linker formed with oligonucleotides SEQ ID NO: 87: CATGGGCGGTGGGGTCAC and SEQ ID NO: 88: TCGAGTGACCCACCGCC. This replaced the first five amino acid residues of a mouse V_H (AQVKL) region present in pCOMB3, with the amino acid sequence GGGS. The light chain leader sequence was similarly modified by inserting a linker formed by oligonucleotides SEQ ID NO: 89: CATGGGGGGAGGCTCA and

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- SEQ ID NO: 90: GATCTGAGCCTCCCCC, together with the Nhe-I/Nco-I fragment of pCOMB 3 via Nhe-I and Bgl-II. This construct was sequenced throughout the modified region, to ensure not only that the modifications were correct, but that the PCR amplified regions had not been subject to Taq polymerase error.

5 The incorporation of a metal co-ordination site composed of six histidines ([His]₆) was accomplished by inserting a phosphorylated linker formed from oligonucleotides SEQ ID NO: 91: CTAGTGCCTAGGTTGGTACCGAGAGGTTC-GCACCATCACCACCATCATG and SEQ ID NO: 92: CTAGCATGATGGTGGTG-ATGG-TGCGAACCTCTCGGTACCAACCTAGGCA into the Nhe-I site. In the
10 resulting construct, the original Nhe-I site is retained, and an Avr-II site has been added 30 nucleotides before the Nhe-I site. The 30 nucleotides between the Avr-II and Nhe-I sites encode Factor Xa (FXa) recognition site and six histidines that form the metal coordination site.

15 Library Construction

Total RNA was prepared from the enriched B-lymphocyte population from a lymph node of a HIV-1 seropositive individual using standard techniques (10). The heavy (γ 1, Fd region) and light chain (κ) immunoglobulin genes in this RNA were
20 amplified as described previously (13) with the single exception of the reverse primers for the heavy chain, which were changed to accommodate the Sfi-I site in vector pL537. These primers were IgG:
GGGCTCGGCCTTCTTGGCCACCTTGGTGTGCT (SEQ ID NO: 93); IgA:
25 GCAGGGGGCCGTCACGGCCTGGGCTGGGATTCGT (SEQ ID NO: 94); IgM:
CACTGGGGCCGGCACGG-CCTTTTCTTTGTTGCCG (SEQ ID NO: 95). K light chains amplified in this way were cloned in to pL537 via Xba-I and Bgl-II (Boehringer-Mannheim, Indianapolis, IN), using 2 μ g of digested vector and 300ng of
30 digested PCR products, ligated overnight at 12°C with T4 ligase (Stratagene, La Jolla, CA) and electroporated into *E.coli* strain DH10B using the Cell-Porator (both from Life Technologies Inc, Gaithersburg, MD). The electroporated DH10Bs were grown in SOC for 1hr at room temperature, then titered in serial 100-fold dilutions (to estimate the size of the libraries) by plating onto LB plates supplemented with 100
35 μ g/mL ampicillin. The remaining bacteria were expanded to a final volume of 500 mL

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- in LB broth containing 100µg/mL ampicillin and 2% D-glucose, and grown overnight at room temperature. Plasmid was prepared from this cultures using standard techniques (10), the κ-chain library was composed of 7×10^5 members. Plasmid prepared from this library was digested with Xho-I and Sfi-I and ligated to similarly digested PCR-amplified Fd fragments, as described for the κ chains. Electroporation, titration and plasmid preparation were performed exactly as described for the κ libraries, and the final library titers were as follows: IgG/κ: 2×10^7 ; IgA/κ: 2×10^6 , IgM/κ: 1×10^6 . The plasmids produced from these constructs were then introduced into *E.coli* XL-1 Blue (Stratagene, La Jolla, CA) and titered as described above. The library of antibody cDNAs in the culture after transformation was then expressed on bacteriophage by superinfection with helper phage M13. These phage preparations were precipitated by addition of 20% volume/volume of a solution containing 20% polyethylene glycol (PEG) 8000 weight/volume and 2.5M NaCl and incubation on ice for 1 hour followed by centrifugation. Phage pellets were resuspended in PBS-T (phosphate buffered saline with 0.05% Tween-20) with 3% BSA added, passed through a 0.2µm filter, titered and used in selection experiments. Titters were typically close to 10^{12} cfu/mL, and restriction digest analysis of colonies from the titer plates indicated that approximately 88% of the phage contained both Fd and κ genes.

Selection of Fab Fragments Binding to gp120

- Wells of a 96-well plate (Costar) were coated with 50 µL of gp120 (Intracell) at 2 µg/mL in carbonate/ bicarbonate buffer, pH 9.4 for 2 hours at 37°C, then blocked with 3% BSA in the same buffer for 2 hours at 37°C, and washed four times with 250µL of PBS-T. The concentrated phage prepared from the libraries were then applied to the wells in a volume of 50 µL, and incubated a room temperature for 2 hours. Unbound phage were then removed by washing 20 times with PBS-T allowing each wash to remain in the well for approximately 3 minutes. Each well was then rinsed twice with PBS before initiating the specific elution of phage recognizing the CD4 binding site of gp120 by adding 50µL of CD4 (duPont) at 100 µg/mL in PBS. After 15 mins of elution, the mixture in the well was removed and the phage present were rescued by incubating the phage/CD4 mixture with 200 µL of *E.coli* XL-1 blue, freshly grown to a density of 0.6 (A_{600}) for 30 minutes at 37°C. 100µL of the resulting

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- cells were plated onto 2xYT plates supplemented with 2% D-glucose, 100 µg/mL ampicillin and 5 µg/mL tetracycline, and grown at 30°C overnight. The resulting colonies were picked, grown in 2xYT medium with 2% D-glucose, 100 µg/mL ampicillin and 5 µg/mL tetracycline and DNA was prepared from the resulting cultures (Wizard minipreps, Promega, Madison, WI). This DNA was digested with Xho-I and Xba-I to determine the presence of a 1.7kB insert, indicating the presence of both Fd and κ chain inserts. Clones containing both Fd and κ chain inserts were converted to soluble Fab expression constructs and sequenced to determine the V-region sequences.

Sequencing of Immunoglobulin Genes

Clones containing inserts were sequenced using standard dideoxy techniques (6, 11). The primers used were as follows: VH forward primer: CCTCACTAAAGGGAACAAAAGCT (SEQ ID NO: 96); VH reverse primer IgM: ATGGAGTCGGGAAGGAAGTCCTGT (SEQ ID NO: 97); VH reverse primer IgG: GTTCGGGGAAGTAGTCCTTGAGGAG (SEQ ID NO: 98); VL forward primer: ACGAATTCTAACTAGCTAGTCGC (SEQ ID NO: 99); VL reverse primer: GGGATAGAAGTTATTCAGCA (SEQ ID NO: 100). The forward primer sequences are based on unique vector sequences approximately 100 nucleotides 5' of the cloning sites for either the Fd fragment or κ chain. The reverse primer sequences are based on the sequence of the appropriate constant region, and located approximately 100 nucleotides 3' of the J/C slice site. Germline gene assignment was performed using Vbase (12).

Expression and purification of soluble Fab fragments

Constructs for the expression of Fab were prepared by digesting the relevant pComb3 construct with Spe-I and Nhe-I and re-ligating, thus eliminating coat protein 3 gene and allowing expression of Fab. Two of the clones isolated contained internal Spe-I sites, but this potential problem was circumvented by isolating the additional fragment, ligating it into the rest of the plasmid, then checking the resulting clones carefully to ensure correct orientation of the insert. Expression of soluble Fab fragments was achieved by growing XL-1 Blue containing the relevant phagemid overnight at 30°C in 2xYT medium containing ampicillin (50 µg/mL), IPTG (1mM) and MgCl₂ (20mM). The bacteria were then harvested by centrifugation, and the

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- release of the Fab fragments was achieved by hypotonic lysozyme treatment using previously described protocols (15). The resulting Fab preparations were purified on anti-Fab columns as previously described (3). Biotinylation was performed using biotin-LC-hydrazide (Pierce, Rockford, IL) in accordance with the manufacturer's instructions.

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Binding Assays

ELISAs were performed using standard methods with recombinant gp120 or viral lysates as antigens. Microtiter plates were coated with antigen in carbonate/ bicarbonate buffer, pH 9.4, at 100ng/well in a volume of 100 μ L. As a positive control, an Fab construct was made containing the V-region genes from F105, a human monoclonal antibody isolated using human hybridoma technology (9). The gene sequences were based on the published sequences of the F105 V-region genes (7), and constructed by overlapping long oligonucleotides by Midland (Austin, TX). These V-region genes were confirmed by sequencing, then subcloned into Fab expression vector pL604 (3) and expressed as Fab fragments as described above. Binding assays were performed with purified, biotinylated Fab fragments detected with Europium (Eu) labelled streptavidin (Wallac, Gaithersburg, MD). Binding was measured using a Wallac 1232 Delphia Research Fluorimeter in accordance with the manufacturer's instructions.

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Deposit of Materials

The phage display libraries of this invention were deposited on June 8, 1999, with the American Type Culture Collection (ATCC). The ATCC accession numbers for the phage display libraries L938, L939 and L944 are PTA-193, PTA-194 and PTA-195, respectively.

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Results

30 Recovery of eluted phage

Seven colonies were recovered from panning with the three phage display libraries for the presence of Fabs that specifically recognized the CD4 binding site of HIV-1 envelope protein gp120. Restriction analysis revealed that six were from the IgG library (Fabs 1-6) and one from the IgM library (Fab 7). The phage isolated from the three libraries were converted to soluble Fab expression plasmids; by

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- digestion of phagemid DNA with Spe-I and Nhe-I followed by re-ligation, thus eliminating the gene for M13 cpIII.

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Sequence Analysis

Initial analysis of the V-region sequences from Fabs 1-7 indicated that they were all different (Figures 1 and 2), and analysis of the C_H1 sequences from Fabs 1-6 showed that they were all IgG₁. Assignment of V-region germline genes indicated that 4 V_H genes were from the V_H3 family (Fabs 1, 3, 5 and 6), 2 were from the V_H4 family (Fabs 2 and 7) and one from the V_H1 family (Fab 4), while 5 of the V_κ genes were from the V_κ 3 family (Fabs 1, 2, 3, 5 and 6) and 2 were from the V_κ 1 family (Fabs 4 and 7). Analysis of J-region gene usage showed that five of the Fabs used JH4b (Fabs 2, 4, 5, 6, and 7) and 2 used JH6b (Fabs 1 and 3), while four used Jk1 (Fabs 2, 3, 4 and 6), two used Jk5 (Fabs 1 and 7) and one used Jk2 (Fab 5). D segment usage could not be determined in 3 cases (Fabs 3, 5 and 6), the other 4 were most closely related to D-segments DXP3 (Fab 1), D3 (Fab 2), D21.9 (Fab 4) and DLR1 (Fab 7). Individual Fab gene assignments are shown in Table 1; the only V_H gene seen in more than one Fab was dp38 (Fabs 1 and 6), but V_κ genes A27 (Fabs 3 and 5) and L6 (Fabs 1 and 6) were both present in 2 Fabs. Alignment of the V_H genes for Fabs 1-7 with the germline genes from which they are putatively derived, showed that the degree of divergence was 0.7% for Fab1, 1.0% for Fabs 2 and 7, 1.4% for Fab4, 2.4% for Fab3 and 2.8% for Fabs 5 and 6 (mean = 2.1%) (Figure 3). Similar analysis for the V_κ sequences indicated that the degree of divergence was 0% for Fab 2, 1.9% for Fabs 4, 5 and 6, 2.3% for Fab 7, 2.6% for Fab1, and 4.9% for Fab3 (mean = 2.2%) (Figure 4).

Table 1

Fab	Isotype	VH-germline	D-segment	JH	Vκ	Jk
1	IgG1/k	3-dp38	DXP4	6b	3-L6	5
2	IgG1/k	4-ep65	D3	4b	3-L2	1
3	IgG1/k	3-dp51	*	6b	3-A27	1
4	IgG1/k	1-dp15	D2.9	4b	1-0122	1
5	IgG1/k	3-dp47	*	4b	3-A27	2
6	IgG1/k	3-dp38	*	4b	3-L6	1
7	IgGM/k	4-VH4-18	DLRI	4b	L-8	5

* = not attributable

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- Binding of Fabs to gp120

First, the binding of biotinylated Fab fragments to the antigen gp120 was examined. In order to assess the relative affinity of these Fab fragments with that of antibodies isolated by more conventional methods, antibody F105, which recognizes the CD4 binding site of HIV-1 gp120, was expressed and purified in the same way as Fabs 1-7. A 2-fold dilution series of each antibody was then tested for binding to gp120 by ELISA. The results of these assays showed that Fabs 1-7 showed that all of the Fabs had binding curves that were similar to F105 (Figure 5). The relative concentration at which 50% binding was observed differed by less than ten-fold across the 8 Fabs tested, with F105 in the middle of the group. Fab 6 gave the strongest binding, with Fabs 1, 4 and F105 showing slightly lower affinities. The Fabs with the lowest relative affinities were Fabs 2 and 7.

The comparison with F105 was extended by binding competition studies, in which the binding of biotinylated Fab fragments to gp120 was competed by unlabelled F105. In these assays, the phage derived Fabs fell into 2 groups; Fabs 1, 5, 6 and 7 showed 50% inhibition of binding by relative F105 Fab concentrations of between 0.2 and 0.5 with Fab 5 showing the most inhibition by F105 (Figure 6). Fabs 2, 3 and 4 showed 50% inhibition of binding by relative F105 Fab concentrations of between 3 and 4 (Figure 6). On the basis of this data, it would appear that Fabs 1-7 fall into 2 groups; those which are readily competed by F105 (Fabs 1, 5, 6 and 7) and those which are relatively resistant to F105 competition (Fabs 2, 3 and 4).

- Competition of Fab Binding by CD4

To further characterize Fabs 1-7, and to confirm the ability of CD4 to compete the binding of these Fabs, and therefore their *de facto* origins, inhibition studies with CD4 were performed. Fab 6 was the least resistant to inhibition by soluble CD4, with 50% inhibition observed at a CD4 concentration of approximately 0.2 µg/mL. Fabs 4 and 7 were most resistant to inhibition by CD4, with 50% inhibition occurring at between 0.7 and 0.8 µg/mL. In this assay F105 Fab showed 50% inhibition at a CD4 concentration of approximately 0.6 µg/mL (Figure 7). Of the remaining Fabs, Fabs 2 and 5 were similar to F105 with 50% inhibition occurring at a CD4 concentration of 0.5 µg/mL, while two, Fabs 1 and 3, showed 50% inhibition at a

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- CD4 concentration of approximately 0.3 µg/mL. Overall, all eight Fabs tested showed broadly similar susceptibility to inhibition by CD4.

Cross Competition between Fabs 1-7

In an attempt to learn something about the similarity of the gp120-Fab interaction for the different Fabs fragments isolated, binding competition experiments were conducted for all of the antibodies. The results of these experiments showed a pattern of moderate inhibition in most cases. There was no competition between Fabs 3 and 5 and very little competition between Fabs 1 and 2. Fabs 1 and 2 generally showed little competition with any of the other Fabs. Fab 3 showed limited competition with any Fabs except 4 and 7. Fab 4 showed competition with Fabs 3, 5 and 6, while Fab 5 showed competition with 4 and 7 and possibly 6. Fab 7 competed with 5 and possibly 3. Fab 6 showed some disagreement between the 2 sides of the assay, but the results indicated some competition with Fabs 3, 4, 5 and 7 (Figure 8). These results suggest that Fabs 3-7 have overlapping binding sites, while Fabs 1 and 2 appear to be largely distinct from this group and from each other.

Strain Specificity

In order to confirm that the Fabs 1-7, selected for their binding to recombinant gp120, were also able to recognize native proteins binding to viral lysates was measured. To obtain information about the ability of these antibodies to recognize multiple strains of HIV-1, binding to three isolates of HIV-1 (IIIb, Ba-L and MN) (5, 8) and one of HIV-2 (isy/sbl) (4) was measured. All of the Fabs reacted most strongly with HIV-1_{IIIb}, probably due to the fact that the recombinant gp120 against which the Fabs were selected was derived from a clone of HIV-1 derived from HIV-1_{IIIb}. The binding to HIV-1_{MN} and HIV-1_{Ba-L} was mixed; only Fab 2 bound about equally well to all three isolates; Fab 3 showed little reactivity to either MN or Ba-L; Fabs 5 and 7 bound to MN at about 50% the level seen with IIIb, but showed little reactivity with Ba-L, while Fab 6 bound Ba-L as well as IIIb but showed no reactivity with MN (Figure 9). The remaining two Fabs (Fabs 1 and 4) bound to both MN and Ba-L at intermediate levels (25-50% of the binding seen with IIIb). Thus, three of the seven Fabs (Fabs 1, 2 and 4) showed relatively strong reactivity with all three isolates of

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- HIV-1 tested, while only one Fab (Fab 3) appeared to be restricted to only IIIb. No binding to HIV-2_{isy/sbl} was seen with any of the Fabs.

The above results demonstrate that the Fab fragments derived from libraries constructed from improved phage vector show significant diversity in the usage of germline genes. In addition, these Fab fragments are similar to anti-gp120 monoclonal antibody F105 in their affinities for gp120. Furthermore, these antibodies competed with CD4 and F105 for binding to gp120, but they showed only limited competition with each other, suggesting that the CD4 binding site of gp120 may overlap several discreet antibody binding sites.

Sequence diversity of the Fab fragments was demonstrated by the isolation of seven different Fab fragments in seven clones. Analysis showed that Fabs 3 and 6 are derived from the same VH and VK germline genes, but the CDR3 regions are clearly different, indicating that they must have been derived from different B-cells. These data are somewhat different from a previous study in which multiple clones were isolated that shared common V-D-J and V-J rearrangements, but which apparently differed in the localization and extent of somatic mutation (2). In addition, the extent of divergence from the nearest germline genes that we observed (between 0 and 5%) is much lower than observed in the previous study (20-30% for most of the sequences) of anti-HIV-1 Fabs derived from phage libraries (2). The levels of somatic mutation in the Fab sequences are, however, very comparable to the levels of somatic mutation described for rearranged human VH genes isolated in conventional ways.

In addition to demonstrating that the Fab antibodies isolated were specific for gp120, the findings presented herein also show that those antibodies recognize native HIV-1 gp120 and that some of them have strain specificity that extends beyond HIV-1_{IIIb}.

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CLAIMS

1. A human monoclonal antibody that is immunoreactive with the HIV-1 glycoprotein gp120, said antibody having heavy (H) and light (L) chain immunoglobulin variable region amino acid sequences selected from the group consisting of SEQ ID NO: 43 through SEQ ID NO: 84.

2. The human monoclonal antibody of claim 1, wherein said antibody has heavy (H) and light (L) chain immunoglobulin variable region amino acid sequences selected from the group consisting of SEQ ID NO: 43 through SEQ ID NO: 56 and is immunoreactive with the CD4 binding site of the HIV-1 glycoprotein gp120.

3. The human monoclonal antibody of claim 1, wherein said antibody has heavy (H) and light (L) chain immunoglobulin variable region amino acid sequences selected from the group consisting of SEQ ID NO: 57 through SEQ ID NO: 72 and is immunoreactive with the V3 loop of the HIV-1 glycoprotein gp120.

4. A human monoclonal antibody according to claim 1, wherein the heavy (H) and light (L) chain immunoglobulin variable region amino acid sequences are encoded by nucleic acid sequences selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 42.

5. A phage display library selected from the group consisting of phage display libraries L938, L939 and L944 having ATCC accession numbers PTA-193, PTA-194 and PTA-195, respectively.

6. A human monoclonal antibody isolated from the phage display library of claim 5.

7. The antibody of claim 6, wherein said antibody is immunoreactive with HIV-1.

8. The antibody of claim 7, wherein said antibody is immunoreactive with HIV glycoprotein gp120.

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9. The antibody of claim 8, wherein said antibody is immunoreactive with the CD4 binding site of the HIV glycoprotein gp120.

10. The antibody of claim 8, wherein said antibody is immunoreactive with the V3 loop of the HIV glycoprotein gp120.

11. A method of detecting HIV-1 in a biological sample, comprising:

(a) contacting the sample with at least one human monoclonal antibody according to claim 1 under conditions suitable to form a complex between the antibody and HIV-1 gp120 protein; and

(b) detecting the presence of said immune complex.

12. A method of detecting HIV-1 in a biological sample, comprising:

(a) contacting the sample with at least one human monoclonal antibody according to claim 7 under conditions suitable to form a complex between the antibody and HIV-1 gp120 protein; and

(b) detecting the presence of said immune complex.

13. The method of claim 11, wherein the biological sample is selected from the group consisting of serum, saliva, lymphocytes or other mononuclear cells.

14. The method of claim 12, wherein the biological sample is selected from the group consisting of serum, saliva, lymphocytes or other mononuclear cells.

15. A pharmaceutical composition comprising at least one human monoclonal antibody according to claim 1 and a suitable excipient, diluent or carrier.

16. A pharmaceutical composition comprising at least one human monoclonal antibody according to claim 7 and a suitable excipient, diluent or carrier.

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◦ 17. The composition of claim 15, further comprising a drug or a gene conjugated to said antibody.

18. The composition of claim 16, further comprising a drug or a gene conjugated to said antibody.

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19. A method of providing passive immunotherapy to a mammal infected with HIV-1 comprising administering to said mammal a therapeutically effective amount of at least one human monoclonal antibody according to claim 1.

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20. A method of providing passive immunotherapy to a mammal infected with HIV-1 comprising administering to said mammal a therapeutically effective amount of at least one human monoclonal antibody according to claim 7.

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21. An anti-idiotypic antibody to the antibody of claim 1.

22. An anti-idiotypic antibody to the antibody of claim 7.

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FIG. 1

Fab1	FR1	CDR1	FR2	CDR2
Fab2	LEVQLQESGGGLVKPGGSLRLS	NAWMS--	WVRQAPGKGLEW	VGRIKSKTDGGTTDYAAPVKGR
Fab3P.....SQT.S.T.TV..GSI.	SGGY.S	.I..H.....	I.Y.YN--S.S.Y.NPSL.S.
Fab4Q.....	TYS.N--	ISY.T.--SSSAIY..DS....
Fab5AEVK...A.V.V..K...Y..	TSYDIN--T.Q....	M.WMNP--NS.NRG..QKFQ..
Fab6V.....Q.....	SYV.T--D.....	.ST.SG--SG.S.Y..DS....
Fab7P.....SET.S.T.TV..GSI.N--T.....P.....
		SSSY.G	.I..P.....	I.SIYY--S.S.Y.NPSL.S.
	FR3		CDR3	FR4
Fab1	FTISRDDSKNTLYLQMNSLKTEDTAVYYCTT		--DPYSSGWYTGYYGMDV	WGQGTITVTVSS
Fab2	V...I.T...KFS.KLS.VTAA.....AR		--AA.-C.F--.DCSF.Y
Fab3NA..S.....RA.....AR		--.L-MG.IFGYS..V..
Fab4	V.MT.NT.IS.A.MELS..RS.....AR		--QG.R.YWVS.-----L.....
Fab5	.M...N...M.....RA.....AK		--.HRRHLF--.D.-D.YL.....
Fab6V.T...QFS.KLS.VTAAY.....AR		L.GRC.YSA.DWCRSF.HL.....
Fab7			---RCT...--VC.GAF.YP.....

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FIG. 2

	FR1	CDR1	FR2	CDR2
Fab1	DLVMTQSPGTLSPGERATLSC	RASQSV-SSYLA	WYQQKPGQAPRLLIY	DASSRAT
Fab2	..Q.....A...V.....-..N..	G..T....
Fab3	...L.....R.....	...L.T.....	...R....
Fab4	..Q.....SS..A.V.D.V.FT.	...SI-..S.NK.K.....	A...LQS
Fab5	...L.....A.....S.Q..	G.....
Fab6	...L.....A.....-.....N....
Fab7	...M.....SF..A.V.D.V.IT.	...GI-.....S.K..K....	GT.I.LQS

	FR3	CDR3	FR4
Fab1	GIPARFSGSGGTFTLTITSSLEPEDFAVYYC	QDCSNWQS	TFGQGTRLDIRR
Fab2E.....QS.....T...	..QTYSTPR	PV.....KVE.K.
Fab3	...D.....	..QYGSSPRKVE.K.
Fab4	V.S.....R.....Y...S.	..Q--SYSRKVE.K.
Fab5	...D.....Q.....T...	..QYGSSPK.E.K.
Fab6R.....	HQY...PPWKVE.K.
Fab7	V.S.....ES.....Q.....T...	..QLNSYPIE.K.

FIG. 3

[illegible]

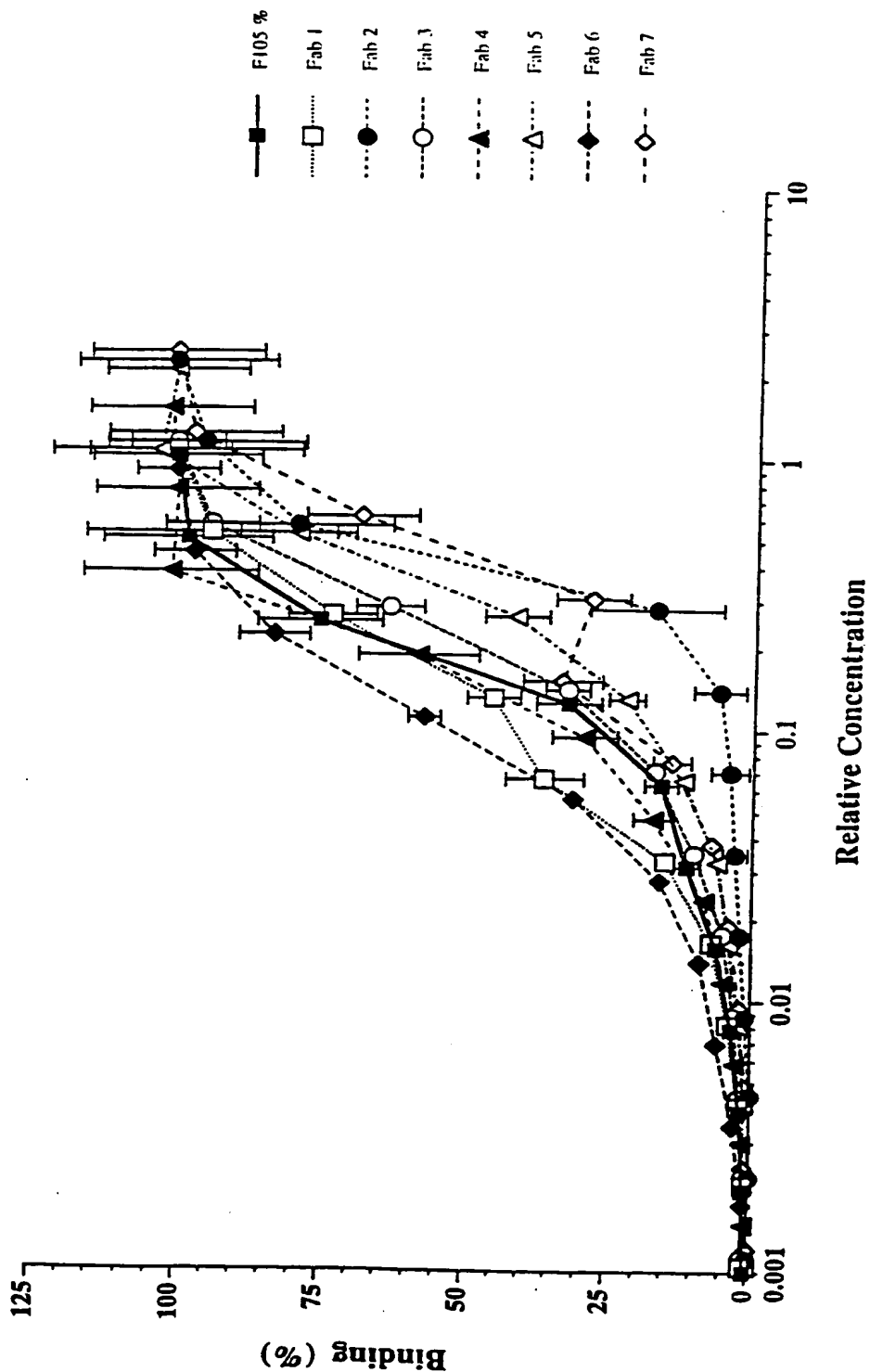
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FIG. 4

L6 Fab1 Fab6	10 GAAATTTGTT ..TC....A ..TC.....G	20 TGAACCAATC ..C.....C	30 TCCAGCCACC CTGTCTTTGT	40 CTGTCTTTGT	50 CTCCAGGGGA AGAGGCCACC CTCTCTCTGA	60 CTCTCTCTGA GGGCCAGTCA GAGTGTTAGC	70 GGGCCAGTCA GAGTGTTAGC AGC---TACT	80 GAGTGTTAGC AGC---TACT	90 GAGTGTTAGC AGC---TACT	100 GAGTGTTAGC AGC---TACT
L2 Fab2	10 GAAATTTGTT ..TC....A ..TC.....G	20 TGAACCAATC ..C.....C	30 TCCAGCCACC CTGTCTTTGT	40 CTGTCTTTGT	50 CTCCAGGGGA AGAGGCCACC CTCTCTCTGA	60 CTCTCTCTGA GGGCCAGTCA GAGTGTTAGC	70 GGGCCAGTCA GAGTGTTAGC AGC---TACT	80 GAGTGTTAGC AGC---TACT	90 GAGTGTTAGC AGC---TACT	100 GAGTGTTAGC AGC---TACT
A27 Fab3 Fab5	10 GAAATTTGTT ..TC....A ..TC.....G	20 TGAACCAATC ..C.....C	30 TCCAGCCACC CTGTCTTTGT	40 CTGTCTTTGT	50 CTCCAGGGGA AGAGGCCACC CTCTCTCTGA	60 CTCTCTCTGA GGGCCAGTCA GAGTGTTAGC	70 GGGCCAGTCA GAGTGTTAGC AGC---TACT	80 GAGTGTTAGC AGC---TACT	90 GAGTGTTAGC AGC---TACT	100 GAGTGTTAGC AGC---TACT
O12/2 Fab4	10 GAAATTTGTT ..TC....A ..TC.....G	20 TGAACCAATC ..C.....C	30 TCCAGCCACC CTGTCTTTGT	40 CTGTCTTTGT	50 CTCCAGGGGA AGAGGCCACC CTCTCTCTGA	60 CTCTCTCTGA GGGCCAGTCA GAGTGTTAGC	70 GGGCCAGTCA GAGTGTTAGC AGC---TACT	80 GAGTGTTAGC AGC---TACT	90 GAGTGTTAGC AGC---TACT	100 GAGTGTTAGC AGC---TACT
L8 Fab7	10 GAAATTTGTT ..TC....A ..TC.....G	20 TGAACCAATC ..C.....C	30 TCCAGCCACC CTGTCTTTGT	40 CTGTCTTTGT	50 CTCCAGGGGA AGAGGCCACC CTCTCTCTGA	60 CTCTCTCTGA GGGCCAGTCA GAGTGTTAGC	70 GGGCCAGTCA GAGTGTTAGC AGC---TACT	80 GAGTGTTAGC AGC---TACT	90 GAGTGTTAGC AGC---TACT	100 GAGTGTTAGC AGC---TACT
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A27 Fab3 Fab5	110 TACCTCTGTAG	120 CCAGCAGAAA CCTGGCCAGGG	130 CCTGGCCAGG CTCCAGGCT	140 CTCCAGGCT CCTCATCTAT	150 CCTCATCTAT GATGCATCCA ACAGGGCCAC	160 GATGCATCCA TGGCATCCCA GCCAGGTTCA	170 TGGCATCCCA GCCAGGTTCA GTGGCAGTGG	180 GCCAGGTTCA GTGGCAGTGG	190 GCCAGGTTCA GTGGCAGTGG	200 GTGGCAGTGG
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L2 Fab2	210 GTCTGGGACA	220 GACTTCACTC	230 TCACCATCAG CAGCCTGCGAG	240 CAGCCTGCGAG CCTGAGATT	250 CCTGAGATT TTGCAAGTTA TTACTGTCAG	260 TTGCAAGTTA TTACTGTCAG CAGCTAGCA	270 TTACTGTCAG CAGCTAGCA ACTGGCCCTCC	280 CAGCTAGCA ACTGGCCCTCC	290 ACTGGCCCTCC	300 ACTGGCCCTCC
A27 Fab3 Fab5	210 GTCTGGGACA	220 GACTTCACTC	230 TCACCATCAG CAGCCTGCGAG	240 CAGCCTGCGAG CCTGAGATT	250 CCTGAGATT TTGCAAGTTA TTACTGTCAG	260 TTGCAAGTTA TTACTGTCAG CAGCTAGCA	270 TTACTGTCAG CAGCTAGCA ACTGGCCCTCC	280 CAGCTAGCA ACTGGCCCTCC	290 ACTGGCCCTCC	300 ACTGGCCCTCC
O12/2 Fab4	210 GTCTGGGACA	220 GACTTCACTC	230 TCACCATCAG CAGCCTGCGAG	240 CAGCCTGCGAG CCTGAGATT	250 CCTGAGATT TTGCAAGTTA TTACTGTCAG	260 TTGCAAGTTA TTACTGTCAG CAGCTAGCA	270 TTACTGTCAG CAGCTAGCA ACTGGCCCTCC	280 CAGCTAGCA ACTGGCCCTCC	290 ACTGGCCCTCC	300 ACTGGCCCTCC
L8 Fab7	210 GTCTGGGACA	220 GACTTCACTC	230 TCACCATCAG CAGCCTGCGAG	240 CAGCCTGCGAG CCTGAGATT	250 CCTGAGATT TTGCAAGTTA TTACTGTCAG	260 TTGCAAGTTA TTACTGTCAG CAGCTAGCA	270 TTACTGTCAG CAGCTAGCA ACTGGCCCTCC	280 CAGCTAGCA ACTGGCCCTCC	290 ACTGGCCCTCC	300 ACTGGCCCTCC

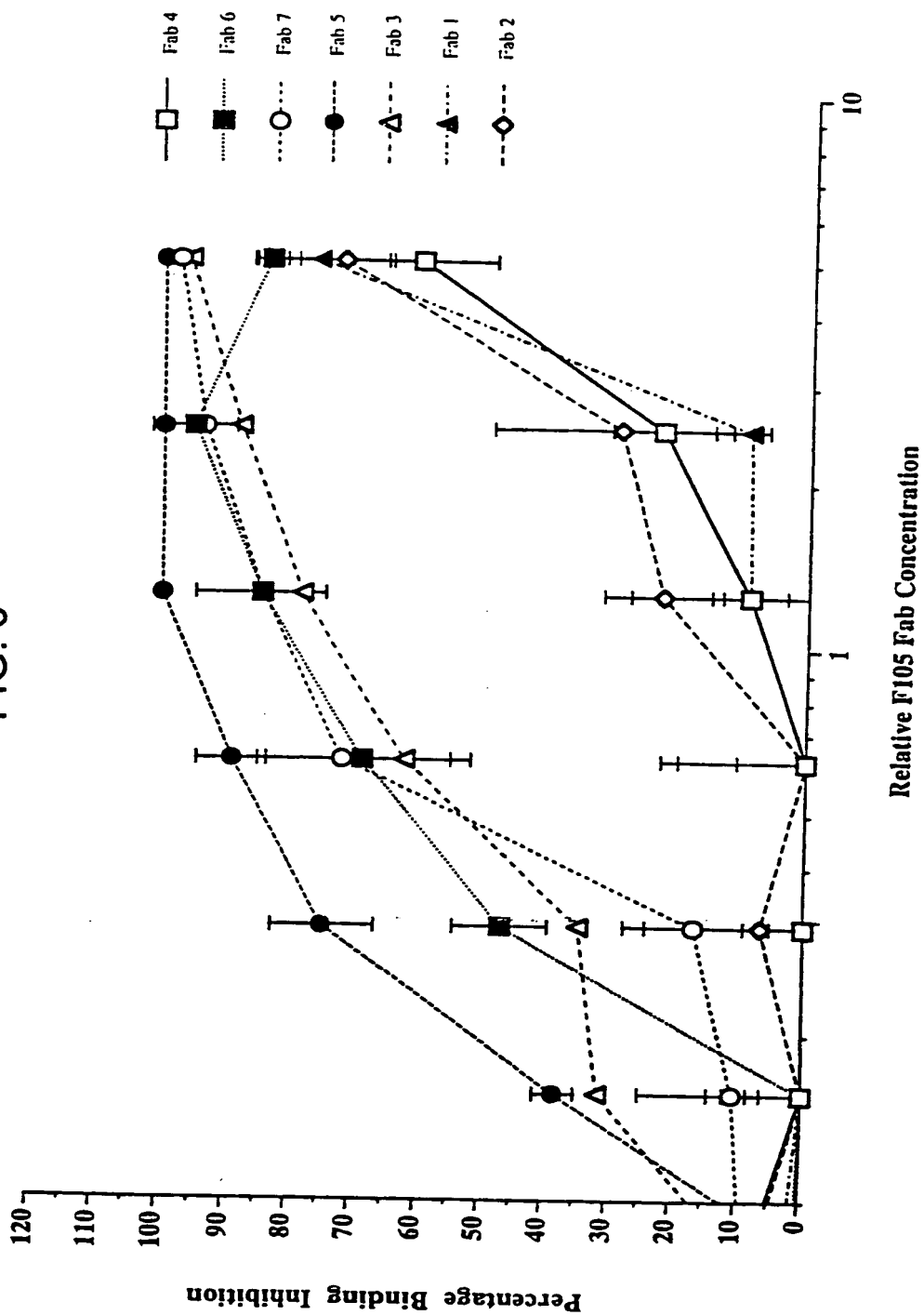
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FIG. 5



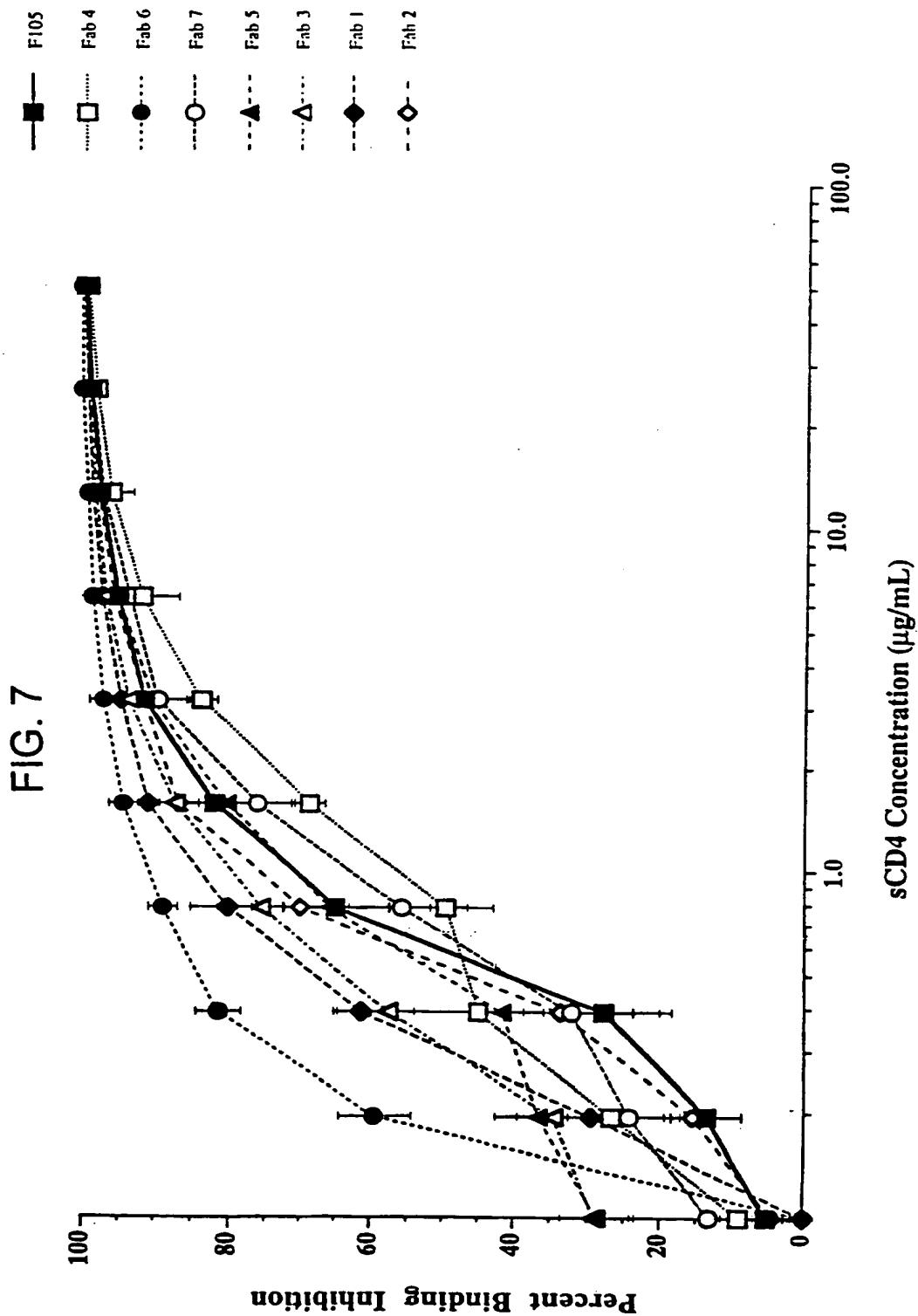
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FIG. 6



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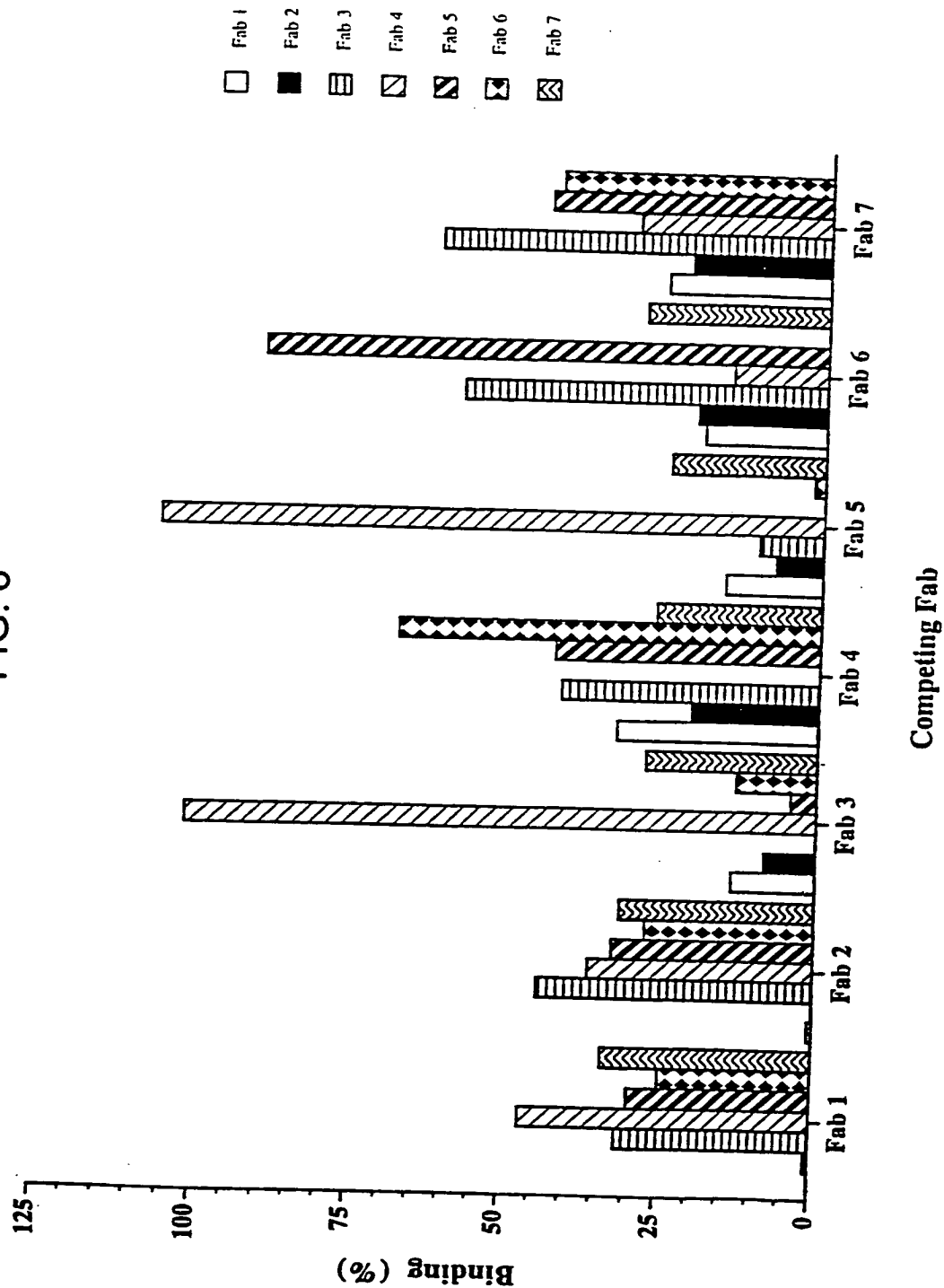
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FIG. 8



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FIG. 9



SEQUENCE LISTING

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Reitz, Jr, Marvin

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caccggcgcc acctcttcgg tgactacgat gactactggg gccagggaac cctgggcacc 360
gtctcctca                                     369

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<210> 6

<211> 390

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 6

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ctcgaggtgc agctgcagga gtcggggggg ggcttggtaa agcctggggg gtcccttaga 60
ctctcctgtg cagcctctgg tttcactttc attaatgcct ggatgaactg ggtccgccag 120
gctccaggga aggggctgga gtgggtcggc cgtattaaaa ccaaaactga tgggtgggaca 180
acagactacc ctgcaccgtg gaaaggcaga ttcaccatct caagagatga ttcaaaaaac 240
acgctgtatc tgcaaatgaa cagcctgaaa accgaggaca cagccgtgta ttactgtacc 300
ttgctcccg gacgttgtgg atatagtgcc tacgattggg gtcgctcctt tgaccactgg 360
ggccaggga ccttggtcac cgtctcctca                                     390

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<210> 7

<211> 372

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 7

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ctcgaggtgc agctgcagga gtcggggcca ggactggtga agccttcgga gaccctgtcc 60
ctcacctgca ctgtctctgg tggtccatc agcagtagta gttactactg gggctggatc 120
cgccagcccc caggaagggt gctggagtgg attgggagta tctattatag tgggagcacc 180
tactacaacc cgtccctcaa gagtcgagtc accatatccg tagacacgtc caagaaccag 240
ttctccctga agctgagctc tgtgaccgcc gcgtacacgg ctgtgtatta ctgtgcgagg 300
cgatgtacta gtggtgtatg ctatggggcc tttgactact ggggccaggg aaccccggtc 360
accgtctcct ca                                     372

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<210> 8
 <211> 324
 <212> DNA
 <213> Human immunodeficiency virus type 1

<220>
 <223> VK

<400> 8
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 ctctcctgca gggccagtca gagggttagc agctacttag cctggtacca acagaaacct 120
 ggccaggctc ccaggctcct catctatgat gcatccagca gggccactgg catcccagcc 180
 aggttcagtg gcagtgggtc tgggacagac ttcaactctca ccatcagcag cctagagcct 240
 gaagattttg cagtttatta ctgtcaagac tgtagcaact ggcagagcac cttcggccag 300
 gggacacgac tggacattag acga 324

<210> 9
 <211> 324
 <212> DNA
 <213> Human immunodeficiency virus type 1

<220>
 <223> VK

<400> 9
 gatctccaga tgacccagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtca gagggttagc agcaacttag cctggtacca gcagaaacct 120
 ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttcaactctca ccatcagcag cctgcagtct 240
 gaagattttg caacttacta ctgtcaacag acttacagta cccctcggcc agtcggccaa 300
 ggaaccaaag tggaaatcaa acga 324

<210> 10
 <211> 327
 <212> DNA
 <213> Human immunodeficiency virus type 1

<220>
 <223> VK

<400> 10
 gatcttgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgta gggccagtca gagggtcaga agcagctact tagcctggta ccagctgaaa 120
 actggccagg ctcccagact cctcatttat gatgcatcca gaagggccac tggcatccca 180
 gacaggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt atgcagtgtg ttcttgtcag caatatggta gttcacctcg gacgttcggc 300
 caagggacca aggtggaaat caaacga 327

<210> 11

<211> 318

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 11

gatctccaga tgacccagtc tccatcctcc ctgtctgcat ctgttggaga cagagtcacc 60
 ttcacttgcc gggcaagtca gagcattagc agctctttaa attggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcagagtgg ggtcccatca 180
 aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagtag tctgcaacct 240
 gaagattttg caacttacta ctgtcaacag agttacagtc ggacgttcgg ccaagggacc 300
 aaggtggaaa tcaaacga 318

<210> 12

<211> 324

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 12

gatctgtgtt tgacgcagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtgtagc agcagccagt tagcctggta tcagcagaaa 120
 cctggccagg ctcccaggct cctcatctac ggtgcatcca gcagggccac tggcatccca 180
 gacaggttca gtggcagtg gtctgggaca gacttcactc tcaccatcag cagactggag 240
 cctgaagatt ttgcagtgtg ttactgtcag cagtatggta gctcaccac ttttggccag 300
 gggaccaagc tggagatcaa acga 324

<210> 13

<211> 327

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 13

gatcttgtgt tgacgcagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

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ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaagcct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcatcag tatagtaact ggccctccgtg gacgttcggc 300
caagggacca aggtggaaat caaacga 327

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<210> 14

<211> 324

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 14

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gatcttgtga tgactcagtc tccctccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gggcattagc agttatttag cctggtatca gcaaaagtca 120
gggaaagccc ctaagctcct gatctatggt acatccattt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa tccactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatagtt acccgatcac cttcggccaa 300
gggacacgac tggagattaa acga 324

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<210> 15

<211> 360

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 15

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ctcgagggtgc agctgcagga gtcggggcgca ggactgttga agccttcgga gaccctgtcc 60
ctcacctgcg ctgtctatgg tgggtccttc agtggttact tctggagctg gatccgcccag 120
ccccaggga aggggctgga gtggattggg gaaatcaatc ctagtggaag caccaactac 180
aaccctgccc tcaagagtcg agtcaccatt tcagttgaca cgtccaagaa ccagttctcc 240
ctgaagctga gctctgtgac cgccgcggac acggctgtgt attactgtgc gagagcaaga 300
atcttcgggt tcggaccatt tgactactgg ggccaggga cctggtcac cgtctcctca 360

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<210> 16

<211> 342

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 16

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ctcgaggtgc agctggtgga gtctggggga ggcttggtcc agcctggggg gtccctgaga 60
ctctactgtg cagcctctgg attcaccttt agcgactatg gcatgaactg ggtccgccag 120
gctccagggga aggggctgga gtgggtctct agtagtggtg ctaccacata ttacgcagac 180
tccgtgaagg gccgggtcac catgtccagg gacaattcca aaaacacgct ctttctgcag 240
atgaacagcc tgagagccga ggacacggcc ctatattact gcgccagggg cattttgcac 300
cccgcctctt gggggccagg aattctgggtc accgtctctt ca 342
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<210> 17

<211> 345

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 17

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ctcgaggtgc agctggtgga gtctggggga ggcttggtcc agcctggggg gtccctgaga 60
ctctcctgtg cagcctctgg attcaccttt agcgactatg gcatgacctg ggtccgccaa 120
gctccagggga aggggctgga gtgggtctct agtagtggtg ctaccacata ttaccagac 180
tccgtgaagg gccgggtcac catgtccagg gacaattcca aaaacacgct ctttctgcag 240
atgaacagcc tcagaccga ggacacggcc ctatattact gtcccagggg cattttgcac 300
ccccggcctc tttggggcca gggcactctg gtcaccgtct cctca 345
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<210> 18

<211> 378

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 18

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ctctcctgtg cagcctctgg attcactttc agtaacgcct ggatgagctg ggtccgccag 120
gctccagggga aggggctgga gtgggttggc cgtattaaaa gcaaaactga tgggtgggaca 180
acagactacg ctgcacccgt gaaaggcaga ttcaccatct caagagatga ttcaaaaaac 240
acgctgtatc tgcaaatgaa cagcctgaaa accgaggaca cagccgtgta ttactgtacc 300
ggggcggtat ggcttcatta cgactactac tatgttatgg acgtctgggg ccaagggacc 360
acggtcaccg tctctca 378
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<210> 19

<211> 369

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 19

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ctcgaggtgc agctgcagga gtcgggggga ggcttggtaa agcctggggg gtcccttaga 60
ctctcctgtg cagcctctgg attcactttc agtaacgcct ggatgagctg ggtccgccag 120
gctccaggga aggggctgga gtgggttggc cgtattaaaa gcaaaactga tgggtgggaca 180
acagactacg ctgcacccgt gaaaggcaga ttcaccatct caagagatga ttcaaaaaaac 240
acgctgtatc tgcaaatgaa cagcctgaaa accgaggaca cagccgtgta ttactgtacc 300
acagccccgg cgcgccccgc tgaatacttc cagcactggg gccagggcac cctgggtcacc 360
gtctcctca
```

369

<210> 20

<211> 387

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 20

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ctcgaggtgc agctgcagga gtcgggagga ggcttggtcc agcctggagg ttccctgaga 60
ctctcctgtg cagcctctgg ttctactttc agtaacgcct ggatgaactg ggtccgccag 120
gctccaggga aggggctgga gttgggttggc cgtaccaaaa gcaaaactga tgggtgggaca 180
acagactaca ctgcacccgt gaaaggcaga ttcaccatct caagagatga ttcaaaaaaac 240
acgctgtatc tgcaaatgaa cagcctgaaa accgaggaca cagccgtgta ttactgtacc 300
acagcccgga tccgacgcag cactatgata gtagaagagg atgcttttga tatctggggc 360
caagggacaa tggtcaccgt ctcttca
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387

<210> 21

<211> 366

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 21

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ctcgaggtgc agctgcagga gtcggggcca ggactggtga agccttcgga gaccctgtcc 60
ctcacctgca ctgtctctgg tgccctccatc agcagtgact actggagctg gatcaggcag 120
ccccaggga agggactgga gtggattggg tatatctatt acagtggggg ccacgtccac 180
aaccctctcc tcacgagtcg agtcaccgtg tcaatggaca agtccaagaa ccagttcgcc 240
ctgaacttga cgtctgtgag cgctgcggac acggccgtct attactgtgc gagatcggac 300
accattccgg tgttccgaaa cggtatggac gtctggggcc aagggaccac gggtcaccgtc 360
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tcctca

366

<210> 22

<211> 366

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 22

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ctcgagggtgc agctgcagga gtcggggccca ggactggtga agccttcaca gaccctgtcc 60
ctcacctgca ctgtctctgg tggctccatc agcagtgggtg gttactactg gagctggatc 120
cgccagcacc caggggaaggg cctggagtgg attgggtaca tctattacag tgggagcacc 180
tactacaacc cgtccctcaa gagtcgagtt accatatcag tagacacgtc taagaaccag 240
ttctccctga agctgagctc tgtgactgcc gcggacacgg ccgtgtatta ctgtgcgagg 300
gacatgctac gggactctac tggactgtgc tactggggcc gtggcaccct ggtcactgtc 360
tcctca

```

366

<210> 23

<211> 327

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 23

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gatcttgtgt tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccagca gggccactgg catcccagac 180
aggtcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag actggagcct 240
gaagattttg cagtgtatta ctgtcagcag tatggtagct cactctcgtg gacgttcggc 300
caagggacca aggtggaaat caaacga

```

327

<210> 24

<211> 330

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 24

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gatcttgtgt tgacgcagtc tccagccacc ctgtgtttgt gtccagggga aagagccacc 60

```

```

ctctcctgca gggccagtga gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcattcca 180
gacagggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggat 240
cctgaagatt ttgcagtgtg ttactgtcag cagtatggtc gctcacccat gtgcagtttt 300
ggccagggga ccaagttgga gatcaaacga                               330

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<210> 25

<211> 327

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 25

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gatcttgtga tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta tcagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtacatcca gcagggccac tggcatcca 180
gacagggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtg ttactgtcag cagtatgcta cttcacctcg gacgttcggc 300
caagggacca aggtggaaat caaacga                               327

```

<210> 26

<211> 339

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 26

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gatcttgtga tgactcagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtgtttta tacagctcca acaataagaa ctacttagct 120
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctaccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gccagcagta ttttaacact 300
cctactttcg gcggagggac caaggtagag atcaaacga                               339

```

<210> 27

<211> 327

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 27

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gatcttgtgt tgacgcagtc tccagggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagggttagc agcatctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgt ttactgtcag cagtatggta gctcaccgtg gacgttcggc 300
caagggacca aggtggaaat caaacga

```

327

<210> 28

<211> 324

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 28

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gatcttgtgt tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagggttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccagca gggccactgg catcccagac 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag actggagcct 240
gaagattttg cagtgtatta ctgtcagcag tatggtagct caccttacac ttttggccag 300
gggaccaagc tggagatcaa acga

```

324

<210> 29

<211> 324

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 29

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gatctccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gaggcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaacctcct gatctatgct gcattcagtt tgcaaagtgg ggtcccagca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagtc cccctcgaac tttcgccct 300
gggaccaaaag tggatatcaa acga

```

324

<210> 30

<211> 327

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 30

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gatcttgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcatctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacagggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtctggta gctcaccgtg gacgttcggc 300
caagggacca aggtggaaat caaacga                                     327

```

<210> 31

<211> 360

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 31

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ctcgaggtgc agctggtgga gtctggagca gaggtgaaaa agcccgggga gtctctgagg 60
atctcctgta agggttcttg atacagcttt accagctact ggatcagctg ggtgcgccag 120
atgcccgga aaggcctgga gtggatgggg aggattgac ctaatgactc ttataccaac 180
tacatcccgt ccttccaagg ccacatcacc atctcagctg acaagtccat caaactgcc 240
tacctgcagt ggagcagcct gaaagcctcg gacaccgcca tgtattactg tgcgagactg 300
aactgaacc aatacgggga gggctactgg ggccagggaa ccctgggtcac cgtctcctca 360

```

<210> 32

<211> 360

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 32

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ctcgaggtgc agctgcagga gtcgggcca ggactggtga agccttcaca gaccctgtcc 60
ctcacctgca ctgtctctgg tggctccatc agcagtgggtg gttactactg gagctggatc 120
cgccagcacc cagggaaagg cctggagtgg attgggtaca tctattacag tgggagcacc 180
tactacaacc cgccctcaa gactcgagtt accatatcag tagacacgtc taagaaccag 240
ttctccctga agctgagctc tgtgactgcc gcggacacgg ccgtgtatta ctgtgcgaga 300
ggggtagtag tggactggtt cgaccctcgg ggccagggaa ccctgggtcac cgtctcctca 360

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<210> 33.

<211> 375
 <212> DNA
 <213> Human immunodeficiency virus type 1

<220>
 <223> VH

<400> 33
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 ctctcctgtg cagcctcttg attcaccttt agtagctatt ggatgagctg ggtccgccag 120
 gctccaggga aggggctgga gtgggtggcc aacataaagc aagatggaag tgagaaatac 180
 tatgtggact ctgtgaaggg ccgattcacc atcttcagaa acaacgcca gaactcactg 240
 tatctgcaaa tgaacagcct gagagccgag gacacggctg tgtattactg tgcgagttgc 300
 tactatggtt cggggagtta ttatttctac ccctttgcct actggggcca gggaaccctg 360
 gtcaccgtct cctca 375

<210> 34
 <211> 369
 <212> DNA
 <213> Human immunodeficiency virus type 1

<220>
 <223> VH

<400> 34
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 ctctcctgtg ctgtctcttg attcaccttc agtagctatt ggatgagctg ggtcatccag 120
 cctccaccga aggggctgga gtgggtgata aggattatcc atcatagagg taacaactac 180
 tatgtggact ctgtcaaggg ccgattcacc atctccatag acaactcca gaactcattg 240
 tacctgcaaa tgaactccct gacagccgaa gacacggccg tgtattactg tgcgagactc 300
 taccaggatt tggagacttc ttatgtctac ggctactggg gccagggaa cctgatcacc 360
 gtctcctca 369

<210> 35
 <211> 375
 <212> DNA
 <213> Human immunodeficiency virus type 1

<220>
 <223> VH

<400> 35
 ctcgaggtgc agctggtgga gtctggggga ggnttggtcc agcctgcggg gtccctgaga 60
 ctctcctgtg cagcctcttg attcaccttt agtagctatt ggatgagctg ggtccgcctc 120
 gctccacgga aggggctgga gtgggtggcc aacatatagc aagatggaag tgagaaatac 180
 tatgtggact ctgtgaaggg ccgattcatc atcttcacat acaacgccta gaactcactg 240

tatctgcaaa tgaacagcct gataaccgag gacacggctg tgtattactg tgctagttgc 300
 tacnntgggt cggggagtta ttatttctac ccctttgcct actggggcca cgggaacctg 360
 gtcacngtct cctca 375

<210> 36

<211> 378

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VH

<400> 36

ctcgaggtgc agctggtgga gtctggggct gaggtgaaga agcctgggtc ctcggtgaag 60
 gtctcctgca aggcctcttg aggcaccttc agcagctatg ctatcagctg ggtgcgacag 120
 gccctggac aagggttga gtggatggga gggatcatcc ctatctttgg tatagcaaac 180
 tacgcacaga agttccaggg cagagtctcg attaccgagg acaaatccac gagcacagcc 240
 tacatggagc tgagcagcct gagatctgag gacacggccg tgtattactg tgcgagagtg 300
 ggaagtatga cgatttttgg agtgggtctcc acgttctttg actactgggg ccaggaacc 360
 ctggtcaccg tctcctca 378

<210> 37

<211> 324

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 37

gatctggtga tgactcagtc tccagccacc ctgtctgtgt cttcagggga aagaaccacc 60
 ctctcctgca gggccagtca gaatgttagc agcaacttag cctggtacca gcagaaacct 120
 gggcaggtc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagac 180
 acattcattg gcagtgggtc tgggacagac ttcactctca ccatcagcag actggagcct 240
 gaagatttag cagtgtatta ctgtcagcaa tatggtagct cacctcggac gttcggccaa 300
 gggaccaagg tggaaatcaa acga 324

<210> 38

<211> 342

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 38

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gatctccaga tgacccagtc tccagacttc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca ggtctagcca gagtgtttta tacagctcca acaataagaa ttacttagct 120
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctatccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg aaacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttataatatt 300
cctccgactt tcggccctgg gaccaaagtg catatcaaac ga 342

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<210> 39

<211> 330

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 39

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gatcttgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagaaccacc 60
ctctcctgca gggccagtc gagtcttagc agcaactact tagcctggta ccagcagaaa 120
cgtggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
aacaggttca gtggcagtgg gtctgggaca aacttcactc tcaccatcag cagactggag 240
cctgaaaatt ttgcagtgta ttattgtcaa cagtatggta gctcacctcc gtacactttt 300
ggccagggga ccaatctgga aatcaaacga 330

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<210> 40

<211> 330

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 40

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gatctcgtga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgca gggccagtc gggcattagc agcgacttaa attggtatca ccagaaacca 120
gggaaagccc ctaagcgct gatctatgct gcatccactt tgcaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacatac ttctctccca ccatcagcag cctgcagcct 240
gaagattatg caacttatta ctgtcgtcaa cattatgggt actctcctcc gacctctttt 300
ggccagggga ctaaactgga aatcaaacgt 330

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<210> 41

<211> 330

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 41

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gatcttgtgt tgacgcagtc tccagacacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtcttagc agcaactact taacctggta ccagcaaaaa 120
cgtggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcaatgg gtctgggaca aacttctctc tcaacatcag cagactggag 240
cctgaaaatt ttgcagtgtg ttattgtcaa cagtatggta gctcacctcc gtacactttt 300
ggccagggga ccaatctgga gatcaaacga                               330

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<210> 42

<211> 324

<212> DNA

<213> Human immunodeficiency virus type 1

<220>

<223> VK

<400> 42

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gatcttgtga tgactcagtc tccatcctcc ctgtctgcag ctgtaggcga cagagtcacc 60
atcacttgcc gggcaagtca gagcataact aattatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatatta ctgtcaacag tatgataatc tccatatcac cttcggccaa 300
gggacacgac tggagattaa acga                               324

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<210> 43

<211> 128

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 43

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Leu Glu Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys Pro Gly
  1              5              10              15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn
      20              25              30

Ala Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
      35              40              45

Val Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala
      50              55              60

Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn

```

65 70 75 80
 Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val
 85 90 95
 Tyr Tyr Cys Thr Thr Asp Pro Tyr Ser Ser Gly Trp Tyr Thr Gly Tyr
 100 105 110
 Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 44
 <211> 123
 <212> PRT
 <213> Human immunodeficiency virus type 1

<400> 44
 Leu Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
 1 5 10 15
 Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser
 20 25 30
 Gly Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu
 35 40 45
 Glu Trp Ile Gly Tyr Ile Tyr Asn Ser Gly Ser Thr Tyr Tyr Asn Pro
 50 55 60
 Ser Leu Lys Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Lys
 65 70 75 80
 Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Ala Arg Ala Ala Tyr Cys Gly Gly Asp Cys Ser Phe Asp Tyr
 100 105 110
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 45
 <211> 125

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 45

Leu Glu Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr
 20 25 30

Tyr Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Ile Ser Tyr Ile Thr Ser Ser Ser Ser Ala Ile Tyr Tyr Ala Asp Ser
 50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
 65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Asp Leu Met Gly Gly Ile Phe Gly Tyr Ser Tyr Gly Val
 100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 46

<211> 120

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 46

Leu Glu Val Gln Leu Gln Glu Ser Gly Ala Glu Val Lys Lys Pro Gly
 1 5 10 15

Ala Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser
 20 25 30

Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp
 35 40 45

Met Gly Trp Met Asn Pro Asn Ser Gly Asn Arg Gly Tyr Ala Gln Lys
 50 55 60

Phe Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala

```
<210> 48
<211> 130
<212> PRT
<213> Human immunodeficiency virus type 1
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<400> 48

Leu Glu Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys Pro Gly
 1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ile Asn
 20 25 30

Ala Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Val Gly Arg Ile Lys Thr Lys Thr Asp Gly Gly Thr Thr Asp Tyr Pro
 50 55 60

Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
 65 70 75 80

Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val
 85 90 95

Tyr Tyr Cys Thr Leu Leu Pro Gly Arg Cys Gly Tyr Ser Ala Tyr Asp
 100 105 110

Trp Cys Arg Ser Phe Asp His Trp Gly Gln Gly Thr Leu Val Thr Val
 115 120 125

Ser Ser
 130

<210> 49

<211> 124

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 49

Leu Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
 1 5 10 15

Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser
 20 25 30

Ser Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
 35 40 45

Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro
 50 55 60

Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln

VSDOCID: <WO_____0100678A1 | >

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ser Thr Pro Arg
 85 90 95

Pro Val Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 52

<211> 109

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 52

Asp Leu Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Leu Lys Thr Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Asp Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80

Pro Glu Asp Tyr Ala Val Tyr Ser Cys Gln Gln Tyr Gly Ser Ser Pro
 85 90 95

Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 53
 <211> 106
 <212> PRT
 <213> Human immunodeficiency virus type 1

<400> 53

Asp Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Phe Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Arg Thr Phe
 85 90 95
 Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 54
 <211> 108
 <212> PRT
 <213> Human immunodeficiency virus type 1

<400> 54

Asp Leu Cys Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 Gln Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

<210> 55

<211> 109

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 55

Asp Leu Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Ser Asn Trp Pro Pro
 85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 56

<211> 108

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 56

Asp Leu Val Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Ser Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Gly Thr Ser Ile Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Glu Ser Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Ile
 85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
 100 105

<210> 57

<211> 120

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 57

Leu Glu Val Gln Leu Gln Glu Ser Gly Ala Gly Leu Leu Lys Pro Ser
 1 5 10 15

Glu Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly
 20 25 30

Tyr Phe Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Ile Gly Glu Ile Asn Pro Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
 50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Ala Arg Ile Phe Gly Phe Gly Pro Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 58

<211> 114

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 58

Leu Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

1

5

10

15

Gly Ser Leu Arg Leu Tyr Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp

20

25

30

Tyr Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp

35

40

45

Val Ser Ser Ser Gly Ala Thr Thr Tyr Tyr Ala Asp Ser Val Lys Gly

50

55

60

Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu Gln

65

70

75

80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg

85

90

95

Gly Ile Leu His Pro Ala Ser Trp Gly Gln Gly Ile Leu Val Thr Val

100

105

110

Ser Ser

<210> 59

<211> 115

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 59

Leu Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

1

5

10

15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp

20

25

30

Tyr Gly Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp

35

40

45

Val Ser Ser Ser Gly Ala Thr Thr Tyr Tyr Pro Asp Ser Val Lys Gly

50

55

60

Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Pro Arg
 85 90 95

Gly Ile Leu His Pro Arg Pro Leu Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110

Val Ser Ser
 115

<210> 60

<211> 126

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 60

Leu Glu Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys Pro Gly
 1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn
 20 25 30

Ala Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Val Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala
 50 55 60

Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
 65 70 75 80

Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val
 85 90 95

Tyr Tyr Cys Thr Gly Ala Val Trp Leu His Tyr Asp Tyr Tyr Tyr Val
 100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 61

<211> 123

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 61

Leu Glu Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys Pro Gly
 1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn
 20 25 30

Ala Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Val Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala
 50 55 60

Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
 65 70 75 80

Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val
 85 90 95

Tyr Tyr Cys Thr Thr Ala Pro Ala Arg Pro Ala Glu Tyr Phe Gln His
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 62

<211> 129

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 62

Leu Glu Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn
 20 25 30

Ala Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu
 35 40 45

Val Gly Arg Thr Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Thr
 50 55 60

Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
 65 70 75 80

Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val
 85 90 95

Tyr Tyr Cys Thr Thr Ala Arg Ile Arg Arg Ser Thr Met Ile Val Glu
 100 105 110

Glu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
 115 120 125

Ser

<210> 63

<211> 122

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 63

Leu Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
 1 5 10 15

Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ala Ser Ile Ser Ser
 20 25 30

Asp Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Ile Gly Tyr Ile Tyr Tyr Ser Gly Gly His Val His Asn Pro Ser Leu
 50 55 60

Thr Ser Arg Val Thr Val Ser Met Asp Lys Ser Lys Asn Gln Phe Ala
 65 70 75 80

Leu Asn Leu Thr Ser Val Ser Ala Ala Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Ser Asp Thr Ile Pro Val Phe Arg Asn Gly Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 64

<211> 122

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 64

Leu Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
 1 5 10 15

Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser
 20 25 30

Gly Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu
 35 40 45

Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro
 50 55 60

Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
 65 70 75 80

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
 85 90 95

Tyr Cys Ala Arg Asp Met Leu Arg Asp Ser Thr Gly Leu Cys Tyr Trp
 100 105 110

Gly Arg Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 65

<211> 109

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 65

Asp Leu Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
 65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Leu Ser
 85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 66

<211> 110

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 66

Asp Leu Val Leu Thr Gln Ser Pro Gly Thr Leu Cys Leu Cys Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Asp
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Pro
 85 90 95

Met Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105 110

<210> 67

<211> 109

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 67

Asp Leu Val Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

35

40

45

Ile Tyr Gly Thr Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ala Thr Ser Pro
 85 90 95

Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 68

<211> 113

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 68

Asp Leu Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
 20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
 85 90 95

Tyr Phe Asn Thr Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

Arg

<210> 69

<211> 108

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 69

Leu Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu
 1 5 10 15

Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ile Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
 65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro Trp
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 70

<211> 107

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 70

Asp Leu Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
 65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro Tyr

85

90

95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 71

<211> 108

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 71

Asp Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Phe Ser Leu Gln Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Pro Pro Arg
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> 72

<211> 109

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 72

Asp Leu Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ile
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Gly Ser Ser Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 73

<211> 119

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 73

Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Asn Asp Ser Tyr Thr Asn Tyr Ile Pro Ser Phe
50 55 60

Gln Gly His Ile Thr Ile Ser Ala Asp Lys Ser Ile Asn Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Leu Thr Leu Asn Gln Tyr Gly Glu Gly Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 74

<211> 120

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 74

Leu Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
1 5 10 15

Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser
20 25 30

Gly Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu
35 40 45

Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro
50 55 60

Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
65 70 75 80

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Gly Val Val Val Asp Trp Phe Asp Pro Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 75

<211> 125

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 75

Leu Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
20 25 30

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Phe Arg Asn Asn Ala Lys Asn Ser Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Ser Cys Tyr Tyr Gly Ser Gly Ser Tyr Tyr Phe Tyr Pro Phe
 100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 76

<211> 123

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 76

Leu Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Ala
 1 5 10 15

Gly Ser Leu Thr Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Ser Ser
 20 25 30

Tyr Trp Met Ser Trp Val Ile Gln Pro Pro Pro Lys Gly Leu Glu Trp
 35 40 45

Val Ile Arg Ile Ile His His Arg Gly Asn Asn Tyr Tyr Val Asp Ser
 50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Ile Asp Asn Ser Lys Asn Ser Leu
 65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Leu Tyr Gln Asp Leu Glu Thr Ser Tyr Val Tyr Gly Tyr
 100 105 110

Trp Gly Gln Gly Thr Leu Ile Thr Val Ser Ser
 115 120

<210> 77

<211> 123

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 77

Leu Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Ala
 1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
 20 25 30

Tyr Trp Met Ser Trp Val Arg Leu Ala Pro Arg Lys Gly Leu Glu Trp
 35 40 45

Val Ala Asn Ile Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
 50 55 60

Lys Gly Arg Phe Ile Ile Phe Thr Tyr Asn Ala Asn Ser Leu Tyr Leu
 65 70 75 80

Gln Met Asn Ser Leu Ile Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95

Ser Cys Tyr Xaa Gly Ser Gly Ser Tyr Tyr Phe Tyr Pro Phe Ala Tyr
 100 105 110

Trp Gly His Gly Asn Leu Val Thr Val Ser Ser
 115 120

<210> 78

<211> 126

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 78

Leu Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly
 1 5 10 15

Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser
 20 25 30

Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
 35 40 45

Met Gly Gly Ile Ile Pro Ile Phe Gly Ile Ala Asn Tyr Ala Gln Lys
 50 55 60

Phe Gln Gly Arg Val Ser Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala
 65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Val Gly Ser Met Thr Ile Phe Gly Val Val Ser Thr Phe
 100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 79

<211> 108

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 79

Asp Leu Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Ser Gly
 1 5 10 15

Glu Arg Thr Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Ser Ser Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Asp Thr Phe Ile Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
 65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro Arg
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 80

<211> 114

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 80

Asp Leu Gln Met Thr Gln Ser Pro Asp Phe Leu Ala Val Ser Leu Gly
 1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Val Leu Tyr Ser
 20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ile Arg Glu Ser Gly Val
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
 85 90 95

Tyr Tyr Asn Ile Pro Pro Thr Phe Gly Pro Gly Thr Lys Val His Ile
 100 105 110

Lys Arg

<210> 81

<211> 110

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 81

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Glu Arg Thr Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Ser Ser Asn
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Arg Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asn Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80

Pro Glu Asn Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
 85 90 95

Pro Tyr Thr Phe Gly Gln Gly Thr Asn Leu Glu Ile Lys Arg
 100 105 110

<210> 82

<211> 110

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 82

Asp Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Asp
 20 25 30

Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Tyr Phe Ser Pro Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Tyr Ala Thr Tyr Tyr Cys Arg Gln His Tyr Gly Tyr Ser Pro
 85 90 95

Pro Thr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105 110

<210> 83

<211> 110

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 83

Asp Leu Val Leu Thr Gln Ser Pro Asp Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Ser Ser Asn
 20 25 30

Tyr Leu Thr Trp Tyr Gln Gln Lys Arg Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Asn Gly Ser Gly Thr Asn Phe Ser Leu Asn Ile Ser Arg Leu Glu
 65 70 75 80

Pro Glu Asn Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
 85 90 95

Pro Tyr Thr Phe Gly Gln Gly Thr Asn Leu Glu Ile Lys Arg
 100 105 110

<210> 84

<211> 108

<212> PRT

<213> Human immunodeficiency virus type 1

<400> 84

Asp Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ala Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Thr Asn Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu His Ile
 85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
 100 105

<210> 85

<211> 33

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 85

ccgcttaact ctagaactga cgagatctgc atg

33

<210> 86

<211> 21

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 86
gtgaaactgc tcgaggtcga c
21

<210> 87
<211> 18
<212> DNA
<213> Human immunodeficiency virus type 1

<400> 87
catgggcggt ggggtcac
18

<210> 88
<211> 17
<212> DNA
<213> Human immunodeficiency virus type 1

<400> 88
tcgagtgacc caccgcc
17

<210> 89
<211> 16
<212> DNA
<213> Human immunodeficiency virus type 1

<400> 89
catgggggga gggtca
16

<210> 90
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<212> DNA
<213> Human immunodeficiency virus type 1

<400> 90
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<210> 91
<211> 49
<212> DNA
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<400> 91
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49

<210> 92

<211> 49

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 92

ctagcatgat ggtggtgatg gtgcgaacct ctcggtacca acctaggca

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<211> 33

<212> DNA

<213> Human immunodeficiency virus type 1

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33

<210> 94

<211> 34

<212> DNA

<213> Human immunodeficiency virus type 1

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gcagggggcc gtcacggcct gggctgggat tcgt

34

<210> 95

<211> 34

<212> DNA

<213> Human immunodeficiency virus type 1

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cactggggcc ggcacggcct tttctttgtt gccg

34

<210> 96

<211> 23

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 96

cctcactaaa gggaacaaaa gct

23

<210> 97

<211> 24

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 97

atggagtcgg gaaggaagtc ctgt

24

<210> 98

<211> 25

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 98

gttcggggaa gtagtccttg aggag

25

<210> 99

<211> 24

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 99

acgaattcta aactagctag tcgc

24

<210> 100

<211> 20

<212> DNA

<213> Human immunodeficiency virus type 1

<400> 100

gggatagaag ttattcagca

20

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17327

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K16/00 G01N33/532 A61K39/395 A61P31/18 //C07K16/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DITZEL H J ET AL: "MAPPING THE PROTEIN SURFACE OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 GP120 USING HUMAN MONOCLONAL ANTIBODIES FROM PHAGE DISPLAY LIBRARIES" JOURNAL OF MOLECULAR BIOLOGY, GB, LONDON, vol. 267, no. 3, March 1997 (1997-03), pages 684-695, XP000885564 ISSN: 0022-2836 abstract page 690 p.692, paragraph bridging left and right column page 693, last paragraph; figure 3 ----- -/--	1-10, 21, 22

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 November 2000

Date of mailing of the international search report

20. 11. 00

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von Ballmoos, P

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 00/17327

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BARBAS C F ET AL: "Molecular profile of an antibody response to HIV-1 as probed by combinatorial libraries." JOURNAL OF MOLECULAR BIOLOGY, (1993 APR 5) 230 (3) 812-23. , XP000942828 abstract page 814, right-hand column, paragraph 2</p>	1-14,21, 22
X	<p>PARREN P W ET AL: "Protection against HIV-1 infection in hu-PBL-SCID mice by passive immunization with a neutralizing human monoclonal antibody against the gp120 CD4 - binding site." AIDS, (1995 JUN) 9 (6) F1-6. , XP000942822 Results section abstract</p>	1,2,4-9, 15-22
X	<p>THOMPSON J ET AL: "Affinity maturation of a high-affinity human monoclonal antibody against the third hypervariable loop of human immunodeficiency virus: use of phage display to improve affinity and broaden strain reactivity." JOURNAL OF MOLECULAR BIOLOGY, (1996 FEB 16) 256 (1) 77-88. , XP000942832 abstract Results section</p>	1,3-8, 10,15-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/17327

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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